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# Contemporary unconventional clinical use of co-trimoxazole

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## Abstract

In the late 1960s, the combination of trimethoprim and sulphamethoxazole (co-trimoxazole) was introduced into clinical practice and used to treat many infectious diseases, such as urinary tract infections, respiratory infections, sexually transmitted diseases, Gram-negative sepsis, enteric infections and typhoid fever. Subsequently, co-trimoxazole was reported to be effective against numerous bacterial, fungal and protozoal pathogens, including *Nocardia*, *Listeria monocytogenes*, *Brucella*, *Stenotrophomonas maltophilia*, *Burkholderia*, *Coxiella burnetii*, *Tropheryma whipplei*, atypical mycobacteria, and *Pneumocystis jirovecii*. Among protozoal infections, in addition to toxoplasmosis, co-trimoxazole has been used to treat susceptible *Plasmodium falciparum*, *Cyclospora* and *Isospora* infections. Several retrospective and prospective studies have demonstrated good clinical outcome with co-trimoxazole in treating invasive methicillin-resistant *Staphylococcus aureus* infections. We summarize herein the accumulated evidence in the literature on the new, 'unconventional' clinical use of co-trimoxazole during the last three decades. In the era of widespread antibiotic resistance and shortage of new antibiotic options, large-scale, well-designed studies are needed to explore the tremendous potential concealed in this well-established drug.

**Keywords:** Bactrim, co-trimoxazole, septrin, trimethoprim–sulphamethoxazole
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## Introduction

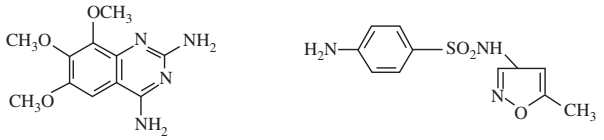
In the era of rapidly escalating antibiotic resistance, along with stagnation of novel antimicrobial production, better compliance with infection control measures and rational use of new antimicrobial agents has become more crucial than ever. In addition, every older antimicrobial agent in our arsenal should be maximally 'squeezed'.

Trimethoprim–sulphamethoxazole (co-trimoxazole) is a well-established compound that is extensively used for various indications in countries with limited resources, offering an additional option in the battle against many pathogens, owing to its low cost, acceptable toxicity profile, availability by both oral and intravenous routes, and bactericidal activity. In the 1930s, a promising new compound was found to possess antimicrobial qualities, especially in animal models. This compound, Prontosil, was one of the first sulphonamide dyes to demonstrate antistreptococcal activity together with a good safety profile [1]. Several modified sulphonamide preparations were produced in later years, improving the safety and specific anti-infectious activity in different sites, such as the central nervous system (CNS), respiratory tract and urinary tract [2].

Trimethoprim was first synthesized during the 1950s, and immediately demonstrated antibacterial activity *in vitro* [3]. During the next decade, it was used in different clinical settings, such as chronic bronchitis, staphylococcal pneumonia, Gram-negative bacteraemia and urinary tract infections [4].

Because of the closely related mechanisms of action, the combination of trimethoprim and sulphamethoxazole (Fig. 1) was investigated immediately, and was found to be synergistic [4].

During the first 2 years of clinical experience, co-trimoxazole was reported to be effective in different clinical conditions, such as urinary tract infections, respiratory tract infections, sexually transmitted diseases, Gram-negative sepsis and typhoid fever [5]. However, widespread use of this drug has led to increasing resistance rates among enteric and respiratory pathogens, peaking during the 1990s [6]. Gradu-




Trimethoprim Sulfamethoxazole

**FIG. 1.** Trimethoprim–sulphamethoxazole molecular structure.

ally, its use in these 'conventional' settings diminished, while other clinical uses were being explored.

During the last three decades, co-trimoxazole re-emerged as an effective treatment for numerous pathogens, including bacteria, fungi and parasites. Its effectiveness has been well documented in some studies, whereas in others the data are sparse and of low quality.

In this review, we present updated data regarding the 'unconventional' use of this drug, other than for nocardiosis, toxoplasmosis and *Pneumocystis jiroveci* pneumonia. Table 1 summarizes the reported literature on the clinical use of co-trimoxazole during the past three decades.

## Bacterial Pathogens

### *Actinomyces*

Evidence of *in vitro* susceptibility of *Actinomyces* to co-trimoxazole exists in the literature [7]. However, very few clinical data are available. Several case series describe successful treatment of actinomycetoma and skin infections with co-trimoxazole [8,9], usually in combination with other drugs, such as penicillin, ampicillin, gentamicin and doxycycline.

### *Aeromonas hydrophila*

*Aeromonas* spp. have good *in vitro* susceptibility to co-trimoxazole [10], although there is a wide range of susceptibility, depending on the specific species and geographical location. There are sparse clinical data showing successful treatment of mainly gastroenteritis and skin and soft tissue infections with co-trimoxazole used as monotherapy [11,12], but they are derived from case series and case reports only.

### *Achromobacter*

This emerging nosocomial pathogen shows over 75% susceptibility to co-trimoxazole *in vitro*. Clinical data consist of small case series [13,14] and case reports demonstrating good clinical outcome in most patients, especially in bacteraemia and urinary tract infection.

### *Stenotrophomonas maltophilia*

This pathogen is a growing threat to hospitalized patients, especially if they are immunosuppressed. Susceptibility to co-trimoxazole has been known and reported for a long time. Clinical information has been derived from numerous case reports, including cases of endocarditis and meningitis. Retrospective studies have demonstrated clinical success in cases of bacteraemia or sepsis [15,16]. A systematic review of skin infections with this pathogen in patients with haematological malignancy demonstrated good cure rates [17]. However, resistance is already developing, and may limit the use of co-trimoxazole in this setting [18].

### *Brucella*

This common zoonotic pathogen has been successfully treated with co-trimoxazole since the 1970s. However, owing to a lack of robust evidence, it is considered to be a second-line treatment [19]. The data derive from many case reports and case series dealing mainly with brucella endocarditis or CNS infection, usually in combination with other drugs such as rifampicin, doxycycline and gentamicin. Several retrospective and prospective studies have demonstrated the efficacy of co-trimoxazole in brucellosis, including in children [20] and pregnant women [21]. Two randomized controlled trials (RCTs) evaluated co-trimoxazole in the treatment of brucellosis. However, in one study, co-trimoxazole was included in both treatment arms [22]. The other study compared six different treatment regimens, including co-trimoxazole alone. All treatment arms were comparable, except for streptomycin plus doxycycline. In light of this information, co-trimoxazole can be considered as a treatment option for brucellosis, especially in pregnant women.

### *Burkholderia*

*Burkholderia cepacia* . This Gram-negative pathogen causes severe infections, especially in patients with cystic fibrosis and chronic granulomatous disease. It is highly resistant to many antibiotics, but *in vitro* data show good sensitivity to co-trimoxazole. Clinical data derive from case reports and case series [23,24] only, and show good clinical response. No large-scale trial was found in the literature.

*Burkholderia pseudomallei* . This is the causative agent of melioidosis. It is a Gram-negative pathogen that is common in Southeast Asia, causing serious infections such as pneumonia, sepsis, intra-abdominal abscesses and skin infections, among both locals and returning travellers. Co-trimoxazole plays an important role in the treatment of this pathogen, although not as monotherapy, as most of the case reports and case series describe drug combinations, especially with ceftazidime. Two RCTs compared different regimens that included co-trimoxazole [25,26]. Another randomized trial compared

**TABLE 1. Summary of the reported literature on the clinical use of co-trimoxazole in the last three decades**

| Pathogen | References: Type | References: No. | Sample size | Presentation | Special population | Comparator | Result | |
|---|---|---|---|---|---|---|---|---|
| Bacterial pathogens | | | | | | | | |
| *Actinomyces* | Case series | 3 | 16 | Actinomycetoma | – | NA | Cure with Cot + Gen + Dox | |
| | | | 7 | Actinomycetoma | – | NA | Cure with Cot + Pen, Gen, Amo | |
| | Case report | 1 | 1 | Cutaneous | – | NA | Cure | |
| *Brucella* | Case series | 6 | 28 | Epididymo-orchitis | – | NA | 75–90% cure with Cot + Rif or Dox | |
| | | | 7 | Endocarditis | – | NA | Cure with Cot + Tet + Strep | |
| | | | 5 | Endocarditis | – | NA | Cure with Cot + Tet + Strep/Gen | |
| | | | 14 | Neurobrucellosis | – | NA | All alive, 8/14 no sequelae with Cot + Rif, Tet, Strep | |
| | | | 33 | Skeletal brucellosis | – | NA | 94% improved, 6% relapsed (Cot with Rif) | |
| | | | 2 | Meningitis | – | NA | Cure with Cot + Rif/Dox | |
| | Retrospective | 2 | 415 | Brucellosis | – | NA | 13.8% relapse with Cot + Rif<br>2.5% relapse with Cot + Dox | |
| | | | 92 | Brucellosis | Pregnant | NA | Protective against spontaneous abortion RR 0.14 (95% CI 0.06–0.37; p <0.0001) | |
| | Case report | 4 | 3 | Endocarditis | – | NA | Cure with Rif and/or Dox/Gen | |
| | | | 1 | Breast abscess | – | NA | Cure with Dox | |
| | Meta-analysis | 1 | 415 | Brucellosis | – | NA | Cot recommended as second line | |
| | RCT | 2 | 280 | Brucellosis | – | Cot + Rif vs. Cot + Dox | Less relapse with Dox than with Rif<br>Cure in 52/64 with Cot | |
| | | | 330 | Brucellosis | – | Cot vs. Dox, Dox + Rif, Dox + Strep | Comparable to all regimens, inferior to Strep + Dox | |
| | Prospective | 1 | 16 | Brucellosis | Children | NA | 100% cure with Cot + Rif | |
| *Listeria* | Case report | 11 | 2 | Brain abscess | Multiple myeloma | NA | Success with Cot + Gen | |
| | | | | | ITP | NA | Success with Cot | |
| | | | 2 | Meningitis | RA | NA | Success with Cot | |
| | | | | | – | NA | Success with Cot | |
| | | | 1 | Vascular graft infection | Aortic graft | NA | Success with Cot + Aug | |
| | | | 1 | Endocarditis | – | NA | Success with Cot + Rif + Tei | |
| | | | 1 | Spinal cord abscess | – | NA | Clinical stabilization with Cot | |
| | | | 1 | Bacteraemia and meningitis | ALL | NA | Improved after Cot was added | |
| | | | 1 | Tenosynovitis | – | NA | Success with Amo + Gen + Cot | |
| | | | 2 | Bacteraemia | AIDS | NA | Success with Cot | |
| | | | | | Liver transplant | NA | Success with Cot | |
| | | | 1 | Osteomyelitis | CLL | NA | Success with Cot | |
| | | | 1 | Septic arthritis | RA | NA | Success with Cot | |
| | | | 1 | Sepsis | Pregnant | NA | Success with Cot + Amp + Gen | |
| | Case series | 1 | 8 | Meningoencephalitis | – | NA | 100% cure with Cot alone | |
| | Case–control | 1 | 90 | Listeriosis | Solid organ transplantation | NA | OR for listeriosis with Cot prophylaxis 0.07 (p 0.029) | |
| | Retrospective | 1 | 22 | Meningoencephalitis | Age, alcohol, lymphoma, leukaemia, myeloma | Amp ± Gen vs. Amp + Cot | 56% failure<br>6.7% failure | 28.5% death<br>6.7% death |
| *Aeromonas* | Case report | 4 | 1 | Pneumonia | Lung transplant | NA | Successful treatment in all cases | |
| | | | 1 | Colitis | MSM | NA | | |
| | | | 1 | Pyomyositis | | NA | | |
| | | | 1 | Gastroenteritis | | NA | | |
| | Case series | 2 | 5 | Foot trauma | – | NA | One received cot as maintenance: successful | |
| | | | 18 | Travellers' diarrhoea | – | NA | Two received Cot: both recovered | |
| *Stenotrophomonas* | Case report | 7 | 1 | VAP | Head injury | NA | Successful treatment but recurrence | |
| | | | | | – | NA | Success | |

**TABLE 1. Continued**

| Pathogen | References | | Sample size | Presentation | Special population | Comparator | Result |
|---|---|---|---|---|---|---|---|
| | Type | No. | | | | | |
| | | | 2 | Endocarditis | VP shunt | NA | Success with Cot + TC |
| | | | 2 | Meningitis | Preterm baby | NA | Success with Cot + Cip |
| | | | | | Neurosurgery | NA | Success with Cot + Cip |
| | | | 1 | Sepsis | Liver transplant | NA | Success with Cot + Min |
| | | | 1 | Peritonitis | Dialysis | NA | Success with Cot + Gen |
| | | | 1 | Osteomyelitis | S/P discectomy | NA | Success with Cot + TC |
| | Retrospective | 2 | 6 | Bacteraemia | HSCT | NA | Success with Cot + Oflo |
| | | | 33 | Sepsis | ICU patients | NA | 45.5% mortality with Cot alone or in combination |
| | Systematic review | 1 | 13 | Skin infections | Haematological malignancy | NA | 9/13 patients recovered with Cot ± Ceft, TC, Cip, Azt, Moxal |
| *Achromobacter* | Case series | 2 | 4 | UTI | – | NA | Two cured, one relapse, one lost to follow-up with Cot |
| | | | 4 | Bacteraemia | Cancer | NA | All responded to treatment |
| | Case report | 1 | 1 | Pulmonary infection | – | NA | Success with Cot + Pip |
| *Burkholderia pseudomallei* | Case report | 11 | 1 | Neck abscess | – | NA | Cure with Ceft, Aug |
| | | | 1 | Pericarditis | – | NA | Cure with Ceft, Dox, Aug |
| | | | 1 | Arthritis | – | NA | Cure with Ceft, Dox, Chlor |
| | | | 2 | Prostatitis | – | NA | Cure with Imi–Ceft, Dox, Aug |
| | | | 1 | Co-infection with *Mycobacterium avium* | – | NA | Cure with Ceft, Dox, Chlor |
| | | | 1 | Osteomyelitis | – | NA | Cure with Ceft, Dox |
| | | | 2 | Lung mass | – | NA | Cure with Ceft ± Dox |
| | | | 1 | Transverse myelitis | – | NA | Cure with Ceft |
| | | | 1 | Adrenal abscess | – | NA | Cure with Ceft |
| | Case series | 3 | 5 | Cranial melioidosis | – | NA | 83% cure with Ceft |
| | | | 2 | Liver abscess | – | NA | Two died with Ceft |
| | | | 9 | Melioidosis | – | NA | All cured with Ceft, Mer, Aug |
| | RCT | 3 | 241 | Severe melioidosis | – | Ceft + Cot vs. Ceft | No difference in mortality, more treatment change with Ceft alone |
| | | | 180 | Melioidosis | – | Cot + Dox vs. Cot + Dox + Chlor | Cot + Dox was as effective and showed more tolerance |
| | | | 102 | Severe melioidosis | – | Cef–Sul + cot vs. Ceft + Cot | No difference in mortality, success or tolerance |
| *Burkholderia cepacia* | Case report | 2 | 1 | Liver abscess | CGD | NA | Success |
| | | | 1 | Meningitis | Infant | NA | Success |
| | Case series | 2 | 3 | Meningitis | Children | NA | Success |
| | | | 5 | Endocarditis | IVDU | NA | Success with polymyxin |
| *Coxiella burnetii* | Retrospective | 2 | 53 | Acute Q-fever | Pregnancy | NA | Long-term Cot therapy decreased obstetric complications, chronic Q-fever and placental infection |
| | | | 20 | Endocarditis | – | NA | Successful treatment in 19/20 with Cot + Tet |
| | Case series | 2 | 3 | Endocarditis | – | NA | Success with Cot + Dox following valve replacement |
| | | | 5 | Endocarditis | – | NA | Success with Cot + Tet |
| | Case report | 1 | 2 | Endocarditis | – | NA | Success with Cot but relapse |
| | | | | Endocarditis | – | NA | Success with Cot + Tet |
| *Tropheryma whipplei* | Case series | 4 | 4 | Endocarditis | – | NA | Success with Cot maintenance following Cef + Gen |
| | | | 2 | Classic Whipple's disease | – | NA | Success with Cot |
| | | | 18 | Endocarditis | – | NA | 16/18 cured with Cot and Ceft, Cip, Dox, Plaq, Van, Gen |
| | | | 12 | Cerebral disease | – | NA | 7/10 improved or stable with Cot + Cef, Amp, Amo, Strep, Dox, Rif |
| | | | 4 | Endocarditis | – | NA | Success with Cot + Cef, Pen, Gen |
| | Case report | 7 | 2 | Endocarditis | – | NA | Success with Cot + Dox + Plaq |
| | | | | | – | NA | Success with Cot + Cef |
| | | | 1 | Cerebral disease | – | NA | Success with Cot + Cef |
| | | | 1 | Ophthalmic | Renal transplant | NA | Success with Cot + Cef + Van |
| | | | 1 | Whipple's disease | – | NA | Failure with Cot, resistance identified. |
| | | | 1 | Cerebral disease | – | NA | Success with Cot + Mer |
| | | | 1 | Cerebral disease | – | NA | Relapse with Cot after 14 months |
| | Prospective cohort | 1 | 14 | Classic Whipple's disease | – | NA | 1/14 died, 3 did not respond to Cot, 10 improved but 5 failed late and 5 relapsed (Gen, Amo, Cef, PT as induction) |
| | RCT | 1 | 40 | Whipple's disease | – | Mer vs. Ceft with Cot maintenance | Cure in 39/40 patients, 1 required change in therapy |
| | Retrospective | 1 | 52 | Whipple's disease | – | NA | Success with 15/16 treated with Cot alone or with Pen + Strep |

**TABLE 1. Continued**

| Pathogen | References: Type | References: No. | Sample size | Presentation | Special population | Comparator | Result |
|---|---|---|---|---|---|---|---|
| Comparative study (retrospective) | | 1 | 30 | Whipple's disease | – | 12 Cot vs. 22 Tet | 1/12 dead with Cot<br>6/22 dead with Tet<br>Success in 12/13 with Cot treatment cycle, and in 13/22 with Tet treatment cycle |
| *Klebsiella Granulomatis (donovanosis)* | Case series | 1 | 10 | Donovanosis | – | NA | Success in all patients |
| | Prospective | 1 | 116 | Donovanosis | – | NA | Success in 100%, recurrence in 2 |
| | Case report | 2 | 1 | Sclerosing granuloma inguinale | – | NA | Success |
| | | | 1 | Penile donovanosis | – | NA | Failure |
| *Staphylococcus aureus* | Retrospective | 7 | 38 | MRSA bacteraemia | – | 38 Cot vs. 76 Van | 25/38 survived with Cot<br>45/76 survived with Van<br>One relapse with Cot, 9 relapses with Van |
| | | | 54 | Skin and soft tissue—CA-MRSA | – | Cot vs. 20 Clin | 26% failure with Cot, 25% failure with Clin |
| | | | 415 | Skin and soft tissue—CA-MRSA | Children | 215 Cot<br>200 Clin | 97.7% did not return to hospital with Cot<br>96.5% did not return to hospital with Clin |
| | | | 6 | Acute otitis media | Children | NA | 6/6 cured with Cot + topical antibiotics |
| | | | 18 | Skin and soft tissue—CA-MRSA | – | NA | 14/18 cured with Cot ± Rif |
| | | | 27 | MRSA infections—skin (15), bacteraemia (4), renal abscess (3), arthritis (2), endocarditis (1), psoas abscess (1), meningitis (1) | – | NA | 26/27 cured with Cot (one bactaeremia failed) |
| | RCT | 7 | 13 | Impetigo | Aboriginal children | 7 Cot vs. 6 Benz Pen | 7/7 cured with cot (5 MSSA and 2 CA-MRSA)<br>5/6 cured with Benz Pen (5 MSSA and 1 CA-MRSA) |
| | | | 190 | Uncomplicated skin abscess | – | 88 Cot vs. 102 placebo (all cases underwent drainage) | 17% failure with Cot<br>26% failure with placebo<br>9% recurrence with Cot<br>28% recurrence with placebo |
| | | | 149 | Uncomplicated skin abscess | Children | 73 Cot vs. 76 placebo (all cases underwent drainage) | 4.1% failure with Cot<br>5.3% failure with placebo<br>12.9% recurrence with Cot<br>26.4% recurrence with placebo |
| | | | 48 | Osteomyelitis | – | 28 Cot + Rif 8 weeks vs. 22 Clox 6 weeks | Success in 24/27 with Cot + Rif<br>Success in 19/21 with Clox |
| | | | 34 | Skin and soft tissue infection | – | 14 (8 MRSA) Cot vs. 20 (15 MRSA) Dox | Success in 6/8 MRSA with Cot<br>Success in 15/15 MRSA with Dox |
| | | | 40 | Ventilated severe burn patients—prophylaxis for MRSA pneumonia | – | 21 Cot<br>19 placebo<br>43 Cot | MRSA pneumonia in 1/21 with Cot, in 7/19 with placebo<br>Success in MSSA:<br>16/22 with Cot, 31/32 with Van |
| | | | 101 | MSSA + MRSA infections | IVDU | 58 Van | Success in MRSA: 21/21 with Cot, 26/26 with Van |
| | Case report | 2 | 2 | Endocarditis | Pregnancy, IVDU | NA | Success only after Cot was added to Van + Rif |
| | | | 1 | Endocarditis | – | NA | Failure with Lin, success with Cot + Gen |
| | Case series | 1 | 2 | Infected bronchiectasis | – | NA | Cure when added to other antibiotics |
| | | | 3 | MRSA meningitis | – | NA | 2/3 survived with Cot + Van |
| | Prospective | 2 | 17 | Infected orthopaedic implants | – | NA | 10/17 cured with Cot alone<br>6/7 cured with implant removal |
| | | | 6 | Osteomyelitis | – | NA | 5/6 cured with Cot |

**TABLE 1. Continued**

| Pathogen | References: Type | References: No. | Sample size | Presentation | Special population | Comparator | Result |
|---|---|---|---|---|---|---|---|
| *Mycobacterium* | Case report | 4 | 1 | *Mycobacterium tuberculosis* | Immunocompromised | NA | Clinical improvement with Cot |
| | | | 1 | Line sepsis with *Mycobacterium fortuitum* | Leukaemia | NA | Cure with Cot + Cip + Ami + Cla |
| | | | 1 | *M. fortuitum* lung abscess | – | NA | Cure with Cot |
| | | | 1 | *M. fortuitum* meningitis | – | NA | Cure with Cot + Rif |
| | Case series | 2 | 2 | *M. fortuitum* skin infection | – | NA | Cure with Cot |
| | | | 3 | Fish tank granuloma—*Mycobacterium marinum* | – | NA | Cure with Cot |
| | Retrospective | 2 | 24 | *M. marinum* skin infection | – | NA | 13/19 improved with Cot |
| | | | 69 | Prophylaxis for *M. avium* complex | HIV | NA | 5/5 improved with Cot + Min<br>6/17 developed MAC infection with Cot prophylaxis<br>34/52 developed MAC infection with no prophylaxis |
| Protozoa | | | | | | | |
| *Acanthamoeba* | Case report | 2 | 1 | CNS abscess | Liver transplant | NA | Cure with Cot + Rif |
| | | | 3 | Meningitis | – | NA | 2/3 survived with Cot + Rif + Ket |
| *Plasmodium* | RCT | 8 | 57 | Uncomplicated *Plasmodium falciparum* | Children | Cot + artesunate vs. Chlo + artesunate | 100% cure both groups |
| | | | 181 | Uncomplicated *P. falciparum* | Children | Cot + artesunate vs. amodiaquine + artesunate | 100% cure both groups |
| | | | 218 | Recurrent uncomplicated malaria | Children | Rif + Cot + Iso vs. mefloquin vs. quinine + SP | Clinical failure 0%, parasitological failure 9%<br>Clinical failure 0%, parasitological failure 0%<br>Clinical failure 1%, parasitological failure 3% |
| | | | 205 | Malaria pneumonia | Children | Cot vs. SP | Clinical and parasitological success 87%<br>Clinical and parasitological success 80% |
| | | | 98 | Uncomplicated *P. falciparum* | Children | Cot (3 days) vs. Cot (5 days) vs. Chlo | Cure rate 88.2%<br>Cure rate 84.8%<br>Cure rate 74.2% |
| | | | 268 | Uncomplicated malaria | Children | Cot vs. SP | Cure rate 96.7%<br>Cure rate 94.5% |
| | | | 61 | Uncomplicated *P. falciparum* | Children | Rif + Cot + Iso vs. chloroquine | 41/41 cured with no recurrence<br>7/20 cured with no recurrence |
| | | | 165 | *Plasmodium vivax* malaria | Children | Cot vs. Chlo | 100% cured with both treatments<br>Faster parasite clearance with Chlor |
| *Isospora* | Case report | 6 | 1 | Diarrhoea | HIV | NA | Death after 1 month |
| | | | 1 | Diarrhoea | Thymoma | NA | Cure with recurrence |
| | | | 1 | Diarrhoea | Intestinal transplant | NA | Cure, no recurrence |
| | | | 1 | Diarrhoea | Liver transplant | NA | Cure, no recurrence |
| | | | 1 | Diarrhoea | Renal transplant | NA | Cure, no recurrence |
| | | | 1 | Diarrhoea | Lymphoma | NA | Cure, no recurrence |
| | Retrospective | 2 | 26 | Diarrhoea | HIV | NA | All cured, 9 relapsed |
| | | | 20 | Diarrhoea | HIV | NA | All cured, 47% recurrence, all responded to Cot |
| | RCT | 2 | 22 | Diarrhoea | HIV | Cot vs. Cip | Cure in 10/10 with Cot |
| | | | 32 | Prophylaxis following *Isospora* diarrhoea | HIV | Cot vs. SP vs. placebo | Cure in 9/12 with Cip, 3 failures cured with Cot<br>No recurrence<br>No recurrence<br>50% recurrence |
| *Cyclospora* | Retrospective | 2 | 6 | Travellers' diarrhoea | – | NA | All cured |
| | | | 7 | Travellers' diarrhoea | – | NA | All cured |
| | Case series | 1 | 5 | Diarrhoea | – | NA | All cured |
| | Case report | 1 | 1 | Diarrhoea | – | NA | Cure |
| | RCT | 3 | 20 | Diarrhoea | HIV | Cot vs. Cip | Cure in 9/9 with Cot<br>Cure in 7/11 with Cip, 4 failures cured with Cot |
| | | | 19 | Diarrhoea | Children | Cot vs. placebo | Shorter time to clinical and parasitological remission with Cot |
| | | | 40 | Diarrhoea | – | Cot vs. placebo | 94% cure with Cot<br>12% cure with placebo |
| | Prospective | 1 | 8 | Travellers' diarrhoea | – | NA | All improved with Cot ± quinolones |

ALL, acute lymphoblastic leukemia; Ami, amikacin; Amo, amoxycillin; Amp, ampicillin; Aug, augmentin; Azt, aztreonam; Benz. Pen., benzathine penicillin; CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; Cef, ceftriaxone; Ceft, ceftazidime; CGD, chronic granulomatous disease; Chlor, chloramphenicol; Chlo, chloroquine; CI, confidence interval; Cip, ciprofloxacin; Cla, clarithromycin; Clin, clindamycin; CLL, chronic lymphocytic leukemia; Clox, cloxacillin; CNS, central nervous system; Cot, co-trimoxazole; Dox, doxycycline; Gen, gentamicin; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplantation; ICU, intensive-care unit; Imi, imipenem; Iso, isoniazid; ITP, idiopathic thrombocytopenic purpura; IVDU, intravenous drug user; Ket, ketoconazole; Lin, linezolid; MAC, mycobacterium avium complex; Mer, meropenem; Min, minocycline; Moxal, moxalactam; MRSA, methicillin-resistant *Staphylococcus aureus*; MSM, men who have sex with men; MSSA, methicillin-sensitive *Staphylococcus aureus*; NA, not assessed; Oflo, ofloxacin; Pen, penicillin; Pip, piperacillin; Plaq, plaquenil; PT, piperacillin–tazobactam; RA, rheumatoid arthritis; Rif, rifampin; RR, relative risk; SP, sulphadoxine–pirimethamine; S/P, status post; Strep, streptomycin; TC, ticarcillin–clavulanate; Tei, teicoplanin; Tet, tetracycline; UTI, urinary tract infection; Van, vancomycin; VAP, ventilator associated pneumonia; VP, ventriculoperitoneal.

the combination of co-trimoxazole and ceftazidime with ceftazidime alone, and found no significant difference in efficacy. However, there were fewer treatment changes with co-trimoxazole.

#### *Listeria monocytogenes*

Since the 1980s, co-trimoxazole has been used successfully in the treatment of *L. monocytogenes*, a Gram-positive bacillus that causes serious infections such as sepsis and meningitis, especially in older and immunosuppressed patients. Case reports and a case series demonstrated efficacy of co-trimoxazole in treating listeriosis, both in combination with other drugs (such as gentamicin, amoxycillin and rifampicin) and as monotherapy. A case–control study in solid organ transplant patients demonstrated that co-trimoxazole prophylaxis was a significant protective factor against listeriosis [27]. A retrospective study in patients with *Listeria* meningoencephalitis demonstrated superiority of co-trimoxazole with ampicillin over gentamicin with ampicillin [28]. Thus, co-trimoxazole is a legitimate option in the treatment of *Listeria* infections.

#### *Coxiella burnetii*

Very few data are available concerning the use of co-trimoxazole in Q-fever. Case reports showed success of co-trimoxazole alone or in combination with tetracyclines in the treatment of Q-fever endocarditis. A retrospective analysis of Q-fever endocarditis demonstrated good cure rates with co-trimoxazole and tetracycline [29]. Another retrospective study demonstrated the efficacy of prolonged co-trimoxazole therapy in pregnant women with acute Q-fever, preventing obstetric complications, chronic Q-fever and placental infection [30]. More data are required to assess the importance of co-trimoxazole in the treatment of Q-fever.

#### *Tropheryma whipplei*

This causative agent of Whipple's disease has been treated with different drug combinations, including co-trimoxazole, especially as long-term maintenance therapy. Numerous case reports and case series showed the efficacy of co-trimoxazole in the treatment of CNS disease and classic Whipple's disease, either alone or in combination with ceftriaxone, or doxycycline and others. One RCT compared meropenem with ceftriaxone as initial treatment of Whipple's disease. Both groups received co-trimoxazole maintenance therapy, with excellent results [31]. Two retrospective studies demonstrated good results with co-trimoxazole alone or in combination with penicillin and streptomycin [32,33]. However, one prospective study [34] and some case reports raised the question of resistance to co-trimoxazole in patients with relapses or failures. Bearing this in mind, co-trimoxazole may still be considered as an important therapeutic option in Whipple's disease.

#### *Klebsiella granulomatis*

Donovanosis is a sexually transmitted disease caused by *K. granulomatis*, formerly known as *Calymmatobacterium granulomatis*. Donovanosis is a rare condition limited to very few geographical locations, such as Papua New Guinea, South Africa, India and Brazil. Successful treatment with co-trimoxazole was documented in the early 1980s, both in a case series [35] and in a prospective study of 116 patients [36]. Although some recurrences and failures were documented in these studies [37], co-trimoxazole is considered to be a second-line choice in the European guidelines for the treatment of donovanosis [38].

### Methicillin-resistant *Staphylococcus aureus* (MRSA)

*S. aureus*, especially MRSA, is one of the most important and problematic pathogens, both in healthcare-associated and in community-acquired infections. The mortality rate of inpatients with *S. aureus* infection is five times higher than in other patients. One of the factors contributing to the high mortality rate is the scarcity of effective and safe treatments, especially in the case of MRSA [39]. The last decade has revealed a growing incidence of community-acquired MRSA, affecting healthy individuals and spreading quickly across the globe.

Co-trimoxazole has been shown to be active against *S. aureus* (including MRSA) *in vitro*. Its components have synergistic bactericidal activity against *S. aureus* [40]. In our centre, the susceptibility of nosocomial bloodstream MRSA isolates to co-trimoxazole increased from 31% in 1988 to 92% in 1997 [41]. The same trends in susceptibility to co-trimoxazole were observed in the USA [42,43].

However, clinical evidence of co-trimoxazole efficacy against MRSA *in vivo* is very limited. There are a few case reports and case series demonstrating the efficacy of co-trimoxazole in MRSA endocarditis and pulmonary infection when used with other drugs. Surprisingly, we found seven randomized controlled trials, seven retrospective studies and two prospective studies evaluating co-trimoxazole in different staphylococcal infections. One RCT demonstrated the efficacy of co-trimoxazole in preventing MRSA pneumonia in severe burn patients [44]. Two other RCTs demonstrated that co-trimoxazole treatment prevented recurrences after drainage of community-acquired MRSA uncomplicated skin abscesses in adults and children [45,46]. Other skin and soft tissue infections and osteomyelitis caused by *S. aureus* were investigated in three RCTs, which indicated equal efficacy with co-trimoxazole and other antibiotics (penicillin, cloxacil-

lin and doxycycline) [47–49]. The only RCT comparing co-trimoxazole with vancomycin was performed in the 1990s on intravenous drug abusers with *S. aureus* bacteraemia. Vancomycin showed superiority in methicillin-sensitive *S. aureus* infections, but was equal to co-trimoxazole in MRSA infections [50]. Several other small retrospective and prospective studies demonstrated good clinical outcome with co-trimoxazole in skin and soft tissue infections, infected orthopaedic implants, osteomyelitis and otitis media. In a retrospective cohort study comparing co-trimoxazole with vancomycin in the treatment of MRSA bacteraemia, we found similar mortality rates in both groups, and a lower relapse rate in the co-trimoxazole group [39]. Overall, it appears that co-trimoxazole is a promising option in treating MRSA, although well-designed RCTs comparing it with vancomycin are required.

#### *Mycobacterium*

*In vitro* susceptibility of different mycobacteria, including *Mycobacterium tuberculosis*, to sulphonamides and subsequently to co-trimoxazole has been investigated for decades, with varying results. However, there are several case reports and case series showing the efficacy of co-trimoxazole in infections with *Mycobacterium fortuitum*, *Mycobacterium marinum* and even *M. tuberculosis* [51]. A retrospective study showed a good clinical response to co-trimoxazole in patients with *M. marinum* skin infections. Another retrospective study demonstrated the efficacy of co-trimoxazole in the prevention of *Mycobacterium avium* complex infections in human immunodeficiency virus (HIV) patients. No prospective trials are available.

## Protozoa

#### Malaria

This common parasite can cause serious infections in adults and children. Evidence of *in vitro* susceptibility to co-trimoxazole, especially for *Plasmodium falciparum*, has existed in the literature for decades. In HIV patients, there is a known relationship between prophylaxis with co-trimoxazole and a decrease in the incidence of malaria [52–54]. Eight RCTs assessed the efficacy of co-trimoxazole in the treatment of malaria, all of them in children, and most of them in uncomplicated *P. falciparum* infections. Two of these studies examined the combination of co-trimoxazole with rifampin and isoniazid in the treatment of uncomplicated malaria. This combination proved to be effective and safe as compared with chloroquine, mefloquine or quinine–sulphadoxine–pyrimethamine [55,56]. Two other studies compared co-trimoxazole–artesunate with other drug combinations (chloroquine–artesunate and amodiaquine–artesunate) in the treatment of uncomplicated *P. falciparum* infections, and showed excellent results in both groups [57,58]. The remaining studies demonstrated equal or superior efficacy of co-trimoxazole alone as compared with chloroquine or sulphadoxine–pyrimethamine in *P. falciparum* [59–61] and *Plasmodium vivax* [62] infections. Although the data are relevant for a specific population, co-trimoxazole is an excellent and relatively unknown treatment option for malaria.

#### *Acanthamoeba*

This parasite can cause devastating CNS infections, with very few effective treatment options. Case reports describing successful treatment usually include combinations of multiple drugs, including co-trimoxazole [63,64].

#### *Isospora belli*

Immunosuppressed individuals, specifically HIV patients, are the target of this parasite, which causes gastrointestinal infections. Co-trimoxazole has been used as a treatment for this pathogen since the 1980s, with several case reports and two retrospective studies demonstrating successful treatment. One small RCT compared co-trimoxazole with ciprofloxacin in HIV patients with isosporiasis, and showed excellent results with co-trimoxazole [65]. Another RCT demonstrated the efficacy of co-trimoxazole in the prevention of isosporiasis after the initial episode in HIV patients [66]. These data are reflected in the CDC guidelines, which recommend co-trimoxazole as the treatment of choice for isosporiasis in HIV patients [67].

#### *Cyclospora*

Adult travellers to endemic areas are the main targets of this pathogen, which is considered to be a cause of traveller's diarrhoea, as well as diarrhoea in immunocompromised hosts. Numerous case reports and a few retrospective and prospective studies showed success with co-trimoxazole in diarrhoea caused by *Cyclospora*. Three RCTs compared co-trimoxazole with ciprofloxacin or placebo for the treatment of *Cyclospora* infections. Co-trimoxazole was an effective treatment, with a low recurrence rate [65,68,69]. This information makes co-trimoxazole a first-line treatment for *Cyclospora* infections.

## Conclusions

Co-trimoxazole is a mixture of trimethoprim and sulphamethoxazole, which act synergistically to produce bacteriostatic

and bactericidal effects against a wide range of Gram-positive and Gram-negative bacteria and some protozoa. Although most information on its efficacy derive from case reports and case series, accumulated data indicate that this old antimicrobial agent has great potential in treating a drug-resistant superbug, MRSA, as well as several other emerging pathogens.

One of the crucial questions is whether the above-mentioned indications will remain anecdotal or whether a real chance exists for the strategic use of this 'forgotten drug'. Large-scale trials are urgently needed to explore the many hidden potentials of this agent.

## Transparency Declaration

Nothing to declare.

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